IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH,	)	
Plaintiffs,	)	
v.	)	C.A. No. 15-1102-GMS
FRESENIUS KABI USA, LLC,	)	**CONSOLIDATED**
Defendant.	)	

DEFENDANT'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases **Page(s)**

Statutes

Other Authorities

TABLE OF ABBREVIATIONS

Abbreviation	Description
§101	35 U.S.C. § 101
'333 patent	**JTX1**, U.S. Patent No. 5,648,333
'7,803 patent	**DTX59**, U.S. Patent No. 5,597,803
'963 patent	**JTX38**, U.S. Patent No. 4,923,963
'993 patent	**JTX28**, U.S. Patent No. 4,693,993
Amino-terminus	The end of a peptide with the free amino group (NH_2), generally written on the left (also known as the N-terminus)
ANDA	Abbreviated New Drug Application
Arg	Arginine (an amino acid)
Barabé	**JTX39**, Barabé & Regoli, *Kinin Antagonists*, 163 Meth. Enzymol. 282 (1988)
Carboxy-terminus	The end of a peptide with the free carboxy group, generally written on the right (also known as the C-terminus)
Chang	**JTX16**, Chang et al., *Solid-Phase Peptide Solid-Phase Peptide Synthesis Using Mild Base Cleavage of Nα-Fluorenylmethyoxucarbonylamino Acids, Exemplified by a Synthesis of Dihydrosomatostatin*, 11 Int. J. Peptide Protein Res. 246 (1978)
D-Arg	The amino acid arginine in the D configuration
D-Phe	The amino acid phenylalanine in the D configuration
D-Pro	The amino acid proline in the D configuration
FDA	United States Food and Drug Administration
Firazyr	Shire's icatibant injection product for subcutaneous use
Fmoc	Fluorenylmethyloxycarbonyl
Fresenius	Defendant Fresenius Kabi USA, LLC

Fresenius's ANDA Product	The product that is the subject of Fresenius's ANDA No. 208317, Icatibant Injection, 30 mg/3 mL prefilled syringe
GATT	Uruguay Round of the General Agreement on Tariffs and Trade, P.L. 103-465.
HAE	Hereditary angioedema
Hoechst	Hoechst Aktiengesellschaft
Nal	Naphthylalanine (an amino acid)
NCE	New Chemical Exclusivity
NDA	New Drug Application
N-terminus	The end of a peptide with the free amine group (NH_2), generally written on the left (also known as amino-terminus)
Nova	Nova Pharmaceutical Corporation
ODE	Orphan Drug Exclusivity
Oic	Cis-endo-octahydroindole-2-carboxylic acid (an amino acid)
ODP	Obviousness-type double patenting
Phe	Phenylalanine (an amino acid)
POSA	Person of ordinary skill in the art
Plaintiffs	Plaintiffs Sanofi-Aventis and Shire, collectively
Pro	Proline (an amino acid)
PTO	United States Patent and Trademark Office
Sanofi-Aventis	Plaintiff Sanofi-Aventis Deutschland GmbH
SAR	Structure-activity relationship
Shire	Plaintiff Shire Orphan Therapies LLC
Thi	Thienylalanine (an amino acid)
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (an amino

	acid)
Wirth 1991	**DTX50**, Wirth *et al.*, *Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vivo Studies*, 102 Br. J. Pharmacol. 774 (1991)
Wirth 1993	**JTX7A.342-346**, Wirth *et al.*, *Effect of Hoe 140 on Bradykinin-induced Bronchoconstriction in Anesthetized Guinea Pigs*, 18 Am. Rev. Respir. Dis. 702 (1993)

DEFENDANT'S TRIAL WITNESSES

Experts

Dr. William Bachovchin

Dr. Bachovchin is currently a Professor of the Department of Developmental, Molecular, and Chemical Biology at Tufts University School of Medicine where he has worked since 1979. Tr. 45:23–46:6, 46:19–47:5; DTX313.
Dr. Bachovchin's research at Tufts has focused on the function and mechanism of protease enzymes. Tr. 47:13-17. His work includes the development of enzyme inhibitors to better understand these enzymes and to develop therapeutic agents. Tr. 48:9-21. He has also worked on making peptides more resistant to proteolytic enzymes and developed a new procedure for stabilizing peptides against degradation. Tr. 51:16-52:1. In addition to his work at Tufts, Dr. Bachovchin founded pharmaceutical companies Point Therapeutics, Inc. and Arisaph Pharmaceuticals, Inc., whose drug products advanced into human clinical trials for treatment of conditions such as diabetes and cardiovascular disease. Tr. 48:25–49:23. He also served on the outside advisory committee of the Stable Isotopes Committee Board of Los Alamos National Laboratory for ten years and has consulted for and received research funding from pharmaceutical companies in connection with his work in peptide chemistry. Tr. 50:7–51:12. Dr. Bachovchin's peptide chemistry research has received funding grants from the NIH and NSF, and he received the Research and Development Award from the NIH. Tr. 52:2-13. He has served as a reviewer for journals including *Nature*, *Science*, *Proceedings for the National Academy of Science*, *Journal of Medicinal Chemistry*, *Biochemistry*, the *Journal of the American Chemical Society*, and others. Tr. 52:21-53:1. In addition, Dr. Bachovchin has published more than 100 journal articles in connection with his work and is a named inventor on more than forty issued U.S. patents and more than 100 patents around the world. Tr. 52:14-20.

Dr. Ronald T. Raines

Dr. Ronald T. Raines is the Firmenich Professor of Chemistry at the Massachusetts Institute of Technology ("MIT"). Tr. 310:19-22. Prior to this appointment, he was the Henry Lardy Professor of Biochemistry, the Linus Pauling Professor of Chemical Biology, and a Professor of Chemistry at the University of Wisconsin–Madison, where he is now Professor Emeritus, and at which he taught many classes relating to biochemistry and organic chemistry. Tr. 310:23-311:9, 312:13-21. Dr. Raines is also the founder of Quintessence Biosciences, Inc., a company focused on development of novel protein based therapeutics as anti-cancer agents, and Hyrax Energy, Inc., which is focused on extracting fermentable sugars from biomass to improve the economics of the cellulosic biofuel pipeline. Tr. 313:11-314:1.

Dr. Raines received Bachelor of Science degrees in Chemistry and Biology from MIT in 1980, and M.A. and Ph.D. degrees in Organic Chemistry from Harvard University in 1982 and 1986, respectively. Tr. 312:2-5. Dr. Raines's research focuses on the structure and function of proteins and peptides and relates to the creation of novel proteins/peptides with desirable properties for potential therapeutic use. Tr. 311:10-18. He has written over 300 peer-reviewed publications of original research and eight book chapters, is the named inventor on fifty-one patents, and has made thirty-nine protein data bank entries. Tr. 314:16-24. Dr. Raines serves on the editorial advisory boards of numerous journals. He has also received numerous awards, including the prestigious Ralph F. Hirschmann Award from the American Chemical Society for his outstanding contribution in the chemistry, biochemistry, or biophysics of peptides, and the Vincent du Vigneaud Award from the American Peptide Society for his outstanding achievements in peptide research. Tr. 314:5-15; DTX316.

Ivan T. Hofmann

Mr. Ivan T. Hofmann is a vice president and managing director at Gleason IP where he leads the intellectual property practice. Tr. 803:16-20; DTX314. In his work, Mr. Hofmann analyzes economic issues in disputes including secondary considerations of nonobviousness, damages, and irreparable harm. Tr. 803:21-804:5. Mr. Hofmann also analyzes licensing, product pipelines, and markets. *Id.* Over the course of his career, Mr. Hofmann has analyzed over one hundred pharmaceutical products, including every major therapeutic class of drugs. Tr. 804:6-10.

Fact Witnesses

Dr. Ronald M. Burch

Dr. Ronald M. Burch is the Chief Executive Officer of Sanguistat, Inc. Tr. 20:2-3. Dr. Burch is an experienced biopharmaceutical executive with a professional career spanning more than 25 years, including nearly two decades of executive experience in the medical device and pharmaceutical industries. Tr. 212:19-215:18. Dr. Burch obtained a Ph.D. in Pharmacology and an M.D. from the Medical University of South Carolina. Tr. 211:24-212:11. Dr. Burch holds B.S. degrees in chemistry and marine biology from the College of Charleston. Tr. 211:13-19. From 1987 to 1991, Dr. Burch served in various capacities at Nova Pharmaceutical Corp., including as Director of Pain and Inflammation, Research Technology. Tr. 210:21-24.

Dr. Irmgard Andresen

Dr. Irmgard Andresen works in the Global Medical Affairs department at Shire. Tr. 796:10-13. She was designated as a 30(b)(6) witness on topics related to the marketing of Firazyr, including but not limited to costs of sales in marketing Firazyr and comparisons to other treatments for acute attacks of hereditary angioedema, and also sales, prescriptions, market share, and forecasts and projections of sales and prescriptions of Firazyr. Tr. 796:18-797:5; DTX120.8.

I. INTRODUCTION

1. The doctrine of obviousness-type double patenting precludes a patentee from obtaining a later-expiring patent claim to an obvious variant of an earlier expiring claim, but that is precisely what happened here. The only asserted claim in this case, Claim 14 of the '333 patent, recites a single peptide sequence of ten amino acids, a sequence called icatibant, which is a bradykinin antagonist. The Plaintiffs own a second patent, however, the '7,803 patent, which claims the *identical* sequence, with an additional "protecting group," called Fmoc, attached to it. The '7,803 patent issued before the '333 patent and is long-expired. The facts presented at trial demonstrated overwhelmingly that a POSA would have been motivated to remove the Fmoc from the icatibant peptide and that doing so would have been a trivial process. Fmoc exists to be removed from peptides. Extensive literature on bradykinin antagonist structures and their activity existed in the prior art, and the evidence at trial showed that a POSA would have reasonably expected the icatibant peptide to be a bradykinin antagonist on the basis of that prior art. Indeed, claim 2 of the '7,803 claims the use of Fmoc-icatibant as a bradykinin antagonist.

2. Plaintiffs' arguments at trial focused on the novelty of the icatibant amino acid sequence, but those arguments are beside the point as Plaintiffs cannot erase the fact that claim 14 of the '333 patent and claim 1 of the '7,803 patent claim the very same underlying peptide sequence. The PTO never addressed the ODP issue because Plaintiffs never brought the '7,803 patent application to the attention of the '333 patent Examiner. And Plaintiffs' secondary considerations evidence cannot salvage the validity claim 14, because Plaintiffs failed to demonstrate a nexus to the merits of the claimed invention. Claim 14 of the '333 patent claims an obvious variant of claim 1 of the '7,803 patent and is therefore invalid for ODP.

3. The invalidity of claim 14 is a problem Plaintiffs foisted on themselves. Although Plaintiffs filed the first '333 patent application years before the first '7,803 patent application, they delayed

the prosecution of the '333 patent for four years. But for that delay the '7,803 patent would not have issued prior to the '333 patent and would not be an ODP reference.

4. Plaintiffs' delay also renders the '333 patent unenforceable for prosecution laches. The trial evidence showed that during the period of prosecution delay, Plaintiffs did not file a single substantive response to an office action, despite having the data requested by the Examiner prior to the original filing. No reason or explanation for the delay was presented at trial. The trial evidence also showed prejudice. At least one competitor was working on bradykinin antagonists covered by the '333 patent during the delay period. And the delay resulted in the patent extending 30 years from the original filing, thus also prejudicing Fresenius by improperly delaying its ANDA approval. Under the Federal Circuit's *Cancer Research* decision, Plaintiffs' unexplained and unreasonable prosecution delay renders the '333 patent unenforceable.

II. PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW ON OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Findings of Fact on Obviousness-Type Double Patenting

1. The Asserted Claim of the '333 Patent

5. The '333 patent relates to bradykinin antagonist peptides. It issued on July 15, 1997, and it expires July 15, 2019. The patent is assigned to Hoechst.[1] Plaintiffs obtained a five-year extension on the '333 patent's statutory patent term, which would have otherwise expired on July 15, 2014. Plaintiffs claim a January 18, 1989 priority date. Claim 14 of the '333 patent, which is the only asserted claim, claims a single ten-amino acid peptide known as icatibant. Tr. 53:18-22, 100:2-4. It reads as follows (JTX1.24):

> 14. A peptide of the formula
> H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH

[1] Hoechst is the predecessor-in-interest to Plaintiff Sanofi-Aventis. Uncontested Facts ¶ 7. Shire is the holder of NDA No. 022150 for Firazyr. *Id.* ¶¶ 10, 12.

or a physiologically tolerable salt of said peptide.

6. The parties' experts agreed that the peptide of claim 14 is unambiguously defined by the sequence of amino acids set out in the claim. Tr. 53:16-22, 99:10–100:7, 555:13-15. There is no dispute that a POSA would have understood the claimed compound based on the claim language.[2] *Id.* Likewise, the experts agreed that the claim term "or physiologically tolerable salts thereof" is unambiguous. Tr. 100:8-21, 554:8-15. Claim 14 does not recite any biological activity, and a POSA would have understood that claim 14 does not require the peptide to have any specific biological activity. Tr. 100:22–101:1, 554:16-18.

2. The '7,803 ODP Reference Patent Claim

7. The '7,803 patent also relates to bradykinin antagonist peptides. It shares five inventors with the '333 patent and is likewise assigned to Hoechst. DTX59.1; JTX1.2; Tr. 98:9-21. Although the application leading to the '7,803 patent was filed *years after* the original application leading to the '333 patent, the '7,803 patent issued on January 28, 1997, *five months before* the issuance of the '333 patent because of applicants' delay in prosecuting the '333 patent. *See* DTX59.1; *see infra* § III. The '7,803 patent expired on January 28, 2014.

8. Claim 1 of the '7,803 patent is directed to a genus of bradykinin analog peptides that have modifications at the so-called "N-terminus." Tr. 101:4-17; *see also* Tr. 510:22–511:5. The group of peptides encompassed by Claim 1 is unambiguous; each peptide is specified by the claim language, and the experts agreed that a POSA could have written out every compound in claim 1.

[2] A person of ordinary skill in the art would have had a Ph.D. in organic chemistry, medicinal chemistry, pharmacology, or a related field, and would have had years of experience in medicinal chemistry or pharmacology related to peptides and experience developing new potential drug candidates. Tr. 55:14-21. This person would also have regularly reviewed the literature related to organic chemistry and medicinal chemistry, including peptide chemistry, and would have been able to analyze and characterize potential drug compounds both structurally and with regard to their biological properties. Tr. 55:22–56:4.

Tr. 101:18-24, 106:22-107:2, 556:19-23. One of those peptides is icatibant, with the addition of an N-terminal Fmoc group, *i.e.*, Fmoc-icatibant. Tr. 107:3-23, 571:18–572:8. The experts agreed that the language of Claim 1 of the '7,803 patent is unambiguous. Tr. 101:18-24, 106:22-107:5, 556:19-23.

9. Although the '7,803 patent specification discloses biological activity for the peptides, claim 1 does not require any particular biological activity. Tr. 101:25–102:2, 556:24–557:23; DTX59.8 Table I (IC_{50} data). Claim 2 of the '7,803 patent claims the use of the peptides as bradykinin antagonists. DTX59.11 at 20:50-55; Tr. 594:1-7, 596:7-11.

3. The Prior Art

a. Background on Peptides and Bradykinin

10. A peptide is a chain of amino acids connected by "peptide bonds." Tr. 99:6-9. Each amino acid has an amino group, a carboxylic acid group, and an "R group," which differs between amino acids and which gives each amino acid its distinct chemical properties. Tr. 56:19–57:17. A peptide is defined by the sequence of amino acids, starting with the amino group of the first amino acid on the left (at the amino- or N-terminus of the peptide) and proceeding along the chain of amino acids to the carboxylic acid group of the last amino acid on the right (which is called the carboxy- or C-terminus of the peptide). Tr. 61:21–63:13.

11. Bradykinin is a naturally occurring peptide in the human body and is made up of nine amino acids. Tr. 61:21–63:13. Bradykinin is involved in several biological effects, including pain, inflammation, and contraction of smooth muscle, and it elicits those effects by binding to the bradykinin receptor. Tr. 79:23–80:10. Bradykinin's effects can become problematic when it is present in excessive quantities. Tr. 82:5–83:4; JTX28.2 at 2:1-8.

12. Because of bradykinin's wide array of biological effects, efforts were undertaken during the 1970s and 1980s to study the effects of bradykinin and to develop bradykinin antagonists,

i.e., compounds that could bind the bradykinin receptor but would not trigger the same biological effects. Tr. 80:11–81:5. The research group of Dr. John Stewart at the University of Colorado led the way in research on bradykinin antagonist peptides. Tr. 81:22–82:4. In the 1970s, Dr. Stewart's group began making "bradykinin analogs," *i.e.*, peptides based on the original nine-amino acid sequence of bradykinin, but in which amino acid substitutions, additions, or deletions have been made. Tr. 63:14-22, 80:11-18; *see* PTX250 (published 1979).

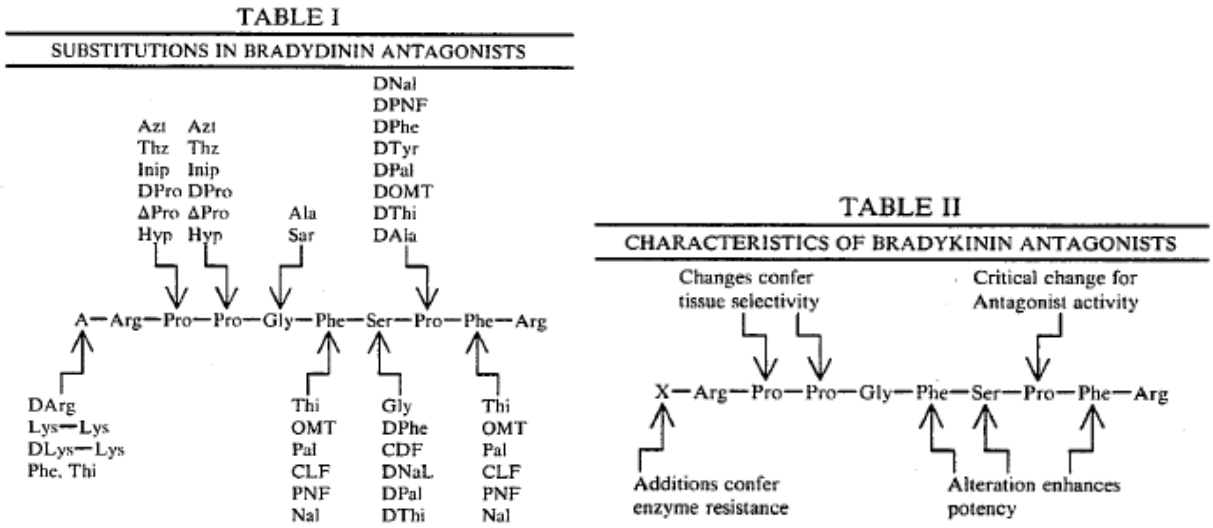
b. The Prior Art Disclosed Bradykinin Antagonists and Structure Activity Relationships For Bradykinin Antagonists

13. By the mid-1980s, Dr. Stewart's lab had identified the first bradykinin antagonists and determined the changes necessary in the bradykinin structure to achieve antagonism, as well as the changes that would increase the peptides' potency, tissue specificity, and resistance to breakdown by enzymes in the body. Tr. 81:11-18. Dr. Stewart applied for a patent disclosing his discoveries in 1985 and obtained a patent in 1987. *See* JTX28.1. Dr. Stewart and his co-workers published extensive prior art on this research throughout the 1980s. *See, e.g.*, JTX25; JTX34; JTX28; JTX30; JTX38.

14. By correlating the activity of their bradykinin analogue peptides in *in vitro* and *in vivo* testing, Dr. Stewart's group developed "structure activity relationship" ("SAR") data. Tr. 85:9–86:12. This SAR data, which was disclosed in the Stewart patents, showed the effects of making changes at various positions within the peptide. Tr. 86:9-14; *see also* JTX28.3, JTX38.3-.4; JTX30.3-.4.

15. Some of Dr. Stewart's SAR data are provided below in Tables I and II of the '993 patent. The sequences A through Arg (Table I) and X through Arg (Table II) depict the natural nine-amino acid sequence of bradykinin, with A and X representing additions that Dr. Stewart and his co-workers made at the N-terminus. Table II identifies the biological effects of substitutions and

additions at the various positions, and Table I provides specific examples of amino acids that Dr. Stewart had determined would cause those effects in bradykinin antagonists.[3] Tr. 86:6–88:3.



16. As shown in Table II, the substitution at position 7 (Pro) was determined to be the "critical change" necessary to create a bradykinin antagonist. Tr. 83:5-21; JTX28.3 at 3:12-30. Dr. Stewart taught that replacing the naturally occurring proline in position 7 of bradykinin with an "aromatic" amino acid of the "D" configuration was the key to creating a bradykinin antagonist. *Id.* As explained at trial, "D" and "L" refer to the stereochemistry (or spatial arrangement) of amino acids, with L being the form found in nature and D being non-natural. Tr. 59:13–60:5; 65:18-21. In Table I, Dr. Stewart listed preferred non-natural D amino acid substitutions in the 7 position of bradykinin antagonists, almost all of which were aromatic.[4]

[3] By convention, the positions of the bradykinin analogues were designated 1 through 9, so that researchers could correlate the position of a substitution with the original amino acid sequence. Additions to the sequence at the N-terminus were designated 0, -1, -2, etc., proceeding from the N-terminal amino acid of bradykinin. Tr. 65:1-17

[4] Dr. Stewart's SAR data indicated a few non-aromatic amino acids that were preferred substitutions as well, such as D-Ala and D-Pro. JTX38.4 ('613 patent Table I). While some of Dr. Stewart's early publications indicated that not all D-aromatic amino acid substitutions worked by themselves to create an antagonist, his later work confirmed that they would result in

Tr. 87:13-88:10; JTX28.3 Tables I & II.

17. Dr. Stewart's SAR also taught the effects of substitutions at other positions. For example, as depicted in Table II, additions to the sequence at position 0 (position X in Table II) conferred resistance to the peptide being broken down by enzymes in the body. Tr. 91:2-13, 94:15-25, 104:11-21; JTX28.3 Tables I & II. Table I lists D-Arg as the first amino acid addition at the N-terminus. JTX28.3 Table I. The addition of D-Arg at the N-terminus provides resistance to degradation by aminopeptidase, an enzyme which would otherwise destroy the peptide by removing the N-terminus. Tr. 203:10-12, 203:21-23.

18. At position 5, Dr. Stewart's SAR data disclosed substitutions (*e.g.*, Thi) that would enhance the potency of antagonists. Tr. 91:24–92:8; JTX28.3 Tables I & II. At position 8, Dr. Stewart's SAR data suggested various substitutions, including the constrained amino acid proline among others. Tr. 122:5-13; JTX38.3 at 4:44-48; JTX28.4 Tables I & II. Another publication co-authored by Dr. Stewart suggested that bulky amino acids, such as cyclohexylalanine, were tolerated in the 8 position. Tr. 123:20–124:12. This prior art SAR data would have served as a non-exhaustive list for predicting the types of substitutions that would be reasonably expected to be effective at each position of a bradykinin antagonist. Tr. 92:9-21.

c. By 1989 Solid-Phase Peptide Synthesis and the Use of Fmoc As a Removable Protecting Group Was Routine

19. By 1989, peptides were synthesized using a process called solid-phase synthesis. Tr. 67:3-7. In this process, a peptide is made by adding one amino acid at a time to the N-terminus of the chain while the other end is attached to a solid support. *See, e.g.*, Tr. 73:14-24. The carboxy group of each amino acid being added forms a peptide bond with the amino group of the last

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antagonism when combined with other substitutions and additions. Tr. 601:19–603:7; JTX28.10-11 at 18:25-30, 18:68–19:19.

amino acid of the peptide chain. *See* Tr. 60:13-22; 73:2-9. As part of this process, the amino group of each amino acid being added must be "protected" from unwanted reactions, meaning that the amino group is bound to a chemical "protecting group" that prevents the amino group from being involved in chemical reactions. Tr. 69:20–70:13. Each time an amino acid is added, the protecting group must be removed from the N-terminus of the growing peptide so that the reaction can take place to form the peptide bond. Tr. 73:10-24. Once the peptide is complete, the last protecting group is removed, and the peptide is cleaved from the resin. Tr. 73:25–74:21. These steps can happen in either order; for instance, the prior art disclosed cleaving the peptide from the resin before removing the protecting group. Tr. 108:16–109:10; JTX16.2.

20. The chemical group Fmoc was one of the most commonly used protecting groups in solid-phase peptide synthesis as of 1989. Tr. 75:7-13, 105:1-4, 297:22-25. Fmoc had an advantage over other protecting groups because of its ease of removal. Tr. 75:17-21, 107:24–108:8 (Fmoc "exists for the purpose of being removed"). Fmoc could be removed from the N-terminus of a peptide by treatment with a mild base, such as piperidine, which did not disturb the rest of the peptide. Tr. 77:5–78:16, 109:3-22, 154:13-17, 155:14-21, 159:14-20, 298:1-6. This is important, as some amino acid R-group side chains need their own protecting groups during synthesis, again to prevent unwanted reactions. Tr. 75:22–76:13. Fmoc could be removed with mild base conditions without removing the side-chain protecting groups on the other amino acids. *Id.*; *see also* Tr. 78:3–78:9; DTX60.3. During peptide synthesis, Fmoc is sometimes removed dozens of times after every amino acid is added to the chain and at the end of synthesis. Tr. 154:17-155:2, 73:10-24; JTX16.2; DTX60.4. Dr. Knolle, one of the named inventors, testified that Fmoc is "always" removed, Tr. 298:13-23:

> Question: And then if you are using Fmoc, for example, to protect the amino acids as they are added, then you have your amino acid sequence with the resin attached at one end and the Fmoc at the other end, right?
>
> Answer: At the end of the synthesis you remove the N-terminal amino protecting group as well and then you cleave it and then you release it. That's how it's done.
>
> Question: And in that answer when you say 'At the end of the synthesis you remove the N-terminal amino protecting group,' you meant you remove the Fmoc, right?
>
> Answer: Always, yes.

21. By 1989, solid-phase peptide synthesis, including Fmoc solid-phase synthesis, was so routine that it was automated; the only difference between making icatibant with Fmoc and without Fmoc was deciding what a POSA wanted to make and programming the machine to make it. Tr. 68:1-9, 573:13-574:10. Dr. Walensky admitted that if a researcher wanted "to make a peptide with the Fmoc on, then I program it that way," but "[i]f I want to make a peptide that has it off, then I program it a different way." Tr. 574:5-8.

4. Claim 1 of the '7,803 Patent Claims Fmoc-Icatibant

22. It is undisputed that Claim 1 of the '7,803 patent discloses and claims Fmoc-icatibant. Positions A through I of the claim represent a nine- or ten-amino-acid peptide. *See* Tr. 101:12-17; DTX59.11. Of these ten positions, only two have more than one option: five options in position A and three options in position G, such that positions A through I define 15 possible peptides. Tr. 102:3–103:25, 556:6-8. The total number of compounds in Claim 1 of the '7,803 patent arises from taking this set of fifteen peptides and making various N-terminal modifications at the Z and/or P positions. *See* Tr. 106:22-24, 556:6-11. Based on the bradykinin antagonist prior art, a POSA would have recognized that positions A through I of Claim 1 constituted a bradykinin antagonist peptide, and that positions Z and P were N-terminal modifications of that peptide. Tr. 101:12-17; 104:1-6.

	POSITIONS Z-P: N-TERMINAL MODIFICATIONS		POSITIONS A – I: BRADYKININ ANTAGONIST									
Claim 1 ('7,803)	N-Protective Genus	Oic; 4-ACHC; Aeg(Fmoc); D-Aoc; Aoc; Bond	Bond; Lys; D-Lys; Arg; D-Arg	Arg	Pro	Hyp	Gly	Thi	Ser	D-Tic	Oic (cis-Exo); Oic (trans); Oic	Arg-OH
Position	**-2 (Z)**	**-1 (P)**	**0 (A)**	**1 (B)**	**2 (C)**	**3 (C)**	**4 (C)**	**5 (E)**	**6 (F)**	**7 (Q)**	**8 (G)**	**9 (F'I)**

23. At the Z position, a POSA would have focused on Fmoc. As discussed above, Fmoc was one of the most widely used protecting groups and had advantages over other such groups in solid-phase peptide synthesis. Tr. 75:7-21, 79:10-19; DTX182.86, 182.165; DTX60.3. A POSA would have recognized the other groups listed in Z to be protecting groups that could be used for peptide synthesis, albeit less effectively than Fmoc in solid-phase synthesis. Tr. 105:5-12; 78:17–79:22; 149:21–150:11.

24. One of the options at the P position is "bond," meaning that the P group can be omitted. Tr. 105:13-18; 106:7-15. Nothing in the prior art suggested that including any of the P groups would provide superior properties. Tr. 106:16-21. The only evidence that Dr. Walensky offered regarding the P groups was based on the testing disclosed in the '7,803 patent specification, Tr. 505:17–509:11, which is not available as prior art. As set forth in the Conclusions of Law, it is legally improper to rely on the specification in an ODP analysis as Shire proposes.

25. There is no dispute that the first option listed for each position of Claim 1 of the '7,803 patent defines a peptide with the identical amino acid sequence of claim 14 of the '333 patent (*i.e.*, icatibant), with an Fmoc protecting group attached to its N-terminus, *i.e.*, Fmoc-icatibant. Tr. 107:6-23, 559:8-25. But the evidence at trial further showed that a POSA would focus on the Fmoc-icatibant sequence in Claim 1, based on the prior art SAR data from the Stewart group and the similarity of the sequence to prior art bradykinin antagonists, including B-3824, one of

Dr. Stewart's leading prior art bradykinin antagonists. Tr. 93:16–95:10, 580:18–581:18.

26. Position A presents five options, but a POSA would have focused on peptides with D-Arg at that position, corresponding to the zero position of the bradykinin antagonist. The POSA would recognize that the prior art SAR data taught the use of a D-Arg at the zero position to "confer enzyme resistance." JTX28.3 Table II; Tr. 104:7-21. D-Arg was known to be a preferred amino acid at the zero position of a bradykinin antagonist for that reason. *Id.* The prior art B-3824 incorporated a D-Arg at position zero. Tr. 93:23-14, 581:7-14.

27. The G position, which corresponds to the 8 position of bradykinin, presents three options, all of which are stereoisomers of the same amino acid: octahydroindole-2-carboxylic acid. Tr. 102:17–103:9. The first listed option is the cis-endo- stereoisomer, known as "Oic". *Id.* No evidence was presented that a POSA would have focused on any option in the G position other than Oic. Furthermore, the substitution of Oic at position 8 is consistent with prior art bradykinin antagonist literature. Tr. 123:20-126:25. Oic was known in the prior art as a bulky, bicyclic amino acid analog of proline. Tr. 120:15-22, 126:11-25, 125:8-17; DTX58.1. Dr. Stewart taught the use of proline at position 8. Tr. 122:5-13, 547:21–548:3; JTX38.3 at 3:66-67, 4:44-48. Like proline, Oic has a five-membered ring that connects back to the peptide backbone, *i.e.*, it is conformationally constrained in the sense that it cannot rotate freely around the peptide backbone. *See* DTX58.1; *see also* Tr. 58:17-22, 126:14-25. In the prior art, bulky, bicyclic, and constrained substitutions at position 8 maintained bradykinin antagonist activity. *Supra* § II(A)(3)(b). The substitution of Oic in position 8 was thus consistent with the prior art. Tr. 125:8-17, 126:14-25.

28. The substitution of D-Tic at position 7 of Fmoc-icatibant was also consistent with the teachings of the prior art. Dr. Stewart's SAR data taught that the critical substitution to generate

bradykinin antagonism was the inclusion of a D-aromatic amino acid at position 7. Tr. 87:20–88:10; JTX28.3 Tables I & II. D-Tic is a D-aromatic amino acid, and a POSA would have reasonably expected it to generate antagonist activity when substituted in the 7 position. Tr. 115:14–116:5. D-Tic was a constrained analog of D-phenylalanine, a well-known position-7 substitution described in the Stewart SAR data and found in prior art antagonists such as B-3824. Tr. 118:1-8, 119:1-17. During this period, researchers at Nova made bradykinin antagonists incorporating D-Tic in position 7 as part of a research strategy to make constrained analogs; Nova scientists expected conformational constraint could confer improved chemical properties on the antagonists. Tr. 223:14-224:21, 614:17–615:4, 635:15–636:21.

5. The Differences Between Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent Are Insubstantial

29. As discussed above, there is no dispute that Claim 1 of the '7,803 patent covers Fmoc-icatibant, which is identical to icatibant except for the addition of an Fmoc protecting group on its N-terminus. Tr. 107:6-23, 559:8-25.

'333 Patent Claim 14 (Icatibant)	D-Arg–Arg–Pro–Hyp–Gly–Thia–Ser–D-Tic–Oic–Arg
'7,803 Patent Claim 1 (Fmoc-icatibant)	Fmoc– D-Arg–Arg–Pro–Hyp–Gly–Thia–Ser–D-Tic–Oic–Arg

As explained below, a POSA starting with Fmoc-icatibant would have been motivated to make icatibant without the Fmoc, *i.e.*, without the Z or P groups. Moreover, the POSA would have had a reasonable expectation that the resulting peptide would be a bradykinin antagonist.

a. A POSA Would Have Been Motivated To Obtain Icatibant Without The N-Terminal Fmoc

30. In analyzing the structure of Fmoc-icatibant, a POSA would look at Fmoc and see first a group used to block the N-terminus of peptides during peptide synthesis. Tr. 107:24–108:8. As Dr. Bachovchin explained, Fmoc-icatibant would appear to a POSA to be a molecule where a

protecting group from synthesis might have simply been left on after synthesis was complete. Tr. 148:14-17.[5]

31. A POSA looking at the Fmoc-icatibant molecule would immediately think of removing the Fmoc, because that is what almost invariably happens at the end of peptide synthesis. *See supra* § II(A)(3)(c); Tr. 107:24–108:8. As Dr. Bachovchin testified, Fmoc "exists for the purpose of being removed." *Id.* It would have been simple to chemically remove the Fmoc from a completed Fmoc-icatibant peptide using the same standard chemistry routinely used in solid-phase peptide synthesis. Tr. 109:11–110:2, 568:12-16. The experts agreed that a POSA could simply have instructed their automated synthesizer to synthesize icatibant without a Z or P group. Tr. 579:12-15, 68:1-14.

32. No evidence was presented at trial that the presence of the Fmoc on Fmoc-icatibant would have been expected to provide any meaningful biological effect. Absent some reason to believe that the N-terminal modification was contributing in a significant way, the POSA would be more interested in the activity of the peptide sequence (*i.e.*, icatibant), which was similar to the ten-amino-acid bradykinin antagonists of the Stewart prior art. Tr. 127:23–128:11. A POSA would be motivated to remove any portion of a peptide that is not contributing significantly to the peptide's desirable properties. *Id.*; Tr. 133:11-22. Plaintiffs presented evidence at trial that certain N-terminal protecting groups can be retained under some circumstances, for some purposes, on some peptides. *See, e.g.*, Tr. 527:11-21. Though such modifications can sometimes have a positive effect, there is no evidence that a POSA would reasonably have expected Fmoc

[5] In fact, as Dr. Walensky explained, this is precisely how the Fmoc-icatibant of the '7,803 patent was synthesized—the patentees performed the same Fmoc-based solid-phase synthesis that would create icatibant, but left the final Fmoc protecting group on the peptide. Tr. 512:16–515:1. The '7,803 patent applicants started with the icatibant sequence in-hand; Fmoc-icatibant is Example 1 of the patent. Tr. 469:13-25; DTX59.9.

(or any of the recited Z or P groups) to have any specific beneficial effect in the claimed bradykinin antagonist peptides. Tr. 127:23–128:11.

b. Plaintiffs' Attempts to Undermine Motivation Fail

33. In response to the facts demonstrating a motivation to remove the Fmoc from Fmoc-icatibant, Plaintiffs' expert, Dr. Walensky, argued for a claim construction in which the POSA would interpret the Z group to be an "integral and permanent component of the final and claimed peptide product." Tr. 500:18-24. According to Dr. Walensky, a POSA would not have been motivated to remove Fmoc because they would view it as intended to be a permanent part of the molecule. Tr. 516:13-17. This opinion was based on, *inter alia*, the claim language, a comparison of claim 1 with claims 2 and 3, and a review of the patent specification and examples. Tr. 509:12-23. None of these assertions withstand scrutiny.

34. Claim 1 of the '7,803 patent does not say that the Z groups are "integral and permanent;" those words are simply not there. Language regarding administration of the peptides and their inclusion in a pharmaceutical composition appears in claims 2 and 3, but it is notably absent from claim 1. Dr. Walensky admitted that claim 1 does not recite any specific activity for the peptides. Tr. 557:18-23. There is no language in claim 1 mandating that the peptides be used in any particular way or precluding their use as intermediates, *i.e.*, using Fmoc-icatibant as an intermediate to make icatibant. *See* Tr. 74:15-21, 107:24–108:12, 109:11-22. Indeed, a POSA would view an Fmoc-protected peptide as an intermediate. *See* Tr. 74:15-21. The suggestion that Fmoc would be viewed by a POSA as "permanent" also flies in the face of Dr. Walensky's eventual admission that Fmoc could be easily removed and that the prior art taught how to do it. Tr. 566:9-20. And Dr. Walensky's position that Fmoc-icatibant would not be viewed as an intermediate is impeached by his reluctant admission on cross-examination that if Fmoc was exposed to base, the Fmoc "would probably fall off." Tr. 568:5-14.

35. Dr. Walensky also offered the opinion that the POSA would not be motivated to remove the Z group because they would expect the addition of the Z group to provide additional biological activity. Tr. 522:5–523:18, 525:4-8. Specifically, Dr. Walensky argued that the addition of the Z-group would provide enzyme resistance, that it could confer bradykinin antagonist activity on the peptide, or that it could reduce the side effect of histamine release from certain antagonists. *Id.* But these arguments fail as well. First, the use of Fmoc in addition to the D-Arg on the N-terminus of Fmoc-icatibant is inconsistent with the teachings of the prior art literature. As Dr. Walensky admitted, the prior art SAR data taught that D-Arg at the zero position was a preferred substitution to provide resistance against degradation by aminopeptidase enzymes. Tr. 520:14-521:4, 522:6-14, 581:25-582:20; JTX38.3-4. The Stewart SAR data suggested that certain protecting groups could be used *instead of* a D-Arg at this position, but it did not suggest or exemplify using an Fmoc or any of the other recited Z or P groups *in addition to* a D-Arg for this purpose. Tr. 128:25–129:19, 132:22–133:7, 585:5-24; JTX38.9–38.11 Tables 4 & 5. Dr. Walensky likewise admitted that the presence of D-Arg at the zero position, without any additional N-terminal groups, comports with the structure of B-3824, which had only a D-Arg on the N-terminus. Tr. 581:7-24. A POSA would not expect the addition of a Z group on the N-terminus of the D-Arg to provide additional protection from aminopeptidases, and because they would see such a group as unnecessary, the POSA would be motivated to remove it or not include it in the first place.

36. Plaintiffs' position on this point is also the opposite of the position they took before the PTO during the prosecution of the '7,803 patent. There, the applicants told the PTO that a POSA *would not expect* peptides with the claimed N-terminal extensions to provide improved biologic activity, and that the activity of the peptides including such extensions was therefore unexpected.

Tr. 778:5–780:14; DTX55.227-228. Here, in the throes of litigation, Plaintiffs assert that a POSA *would expect* the N-terminal protecting group to provide improved biologic activity, and that they would therefore not be motivated to remove it. Tr. 522:6–523:18, 525:4-8. Plaintiffs cannot have it both ways. The evidence at trial demonstrated that the POSA would not have expected that leaving the Z or P groups attached would provide an improved biological effect, as Plaintiffs told the PTO before this litigation started.

37. Finally, Plaintiffs rely on the Barabé paper in an effort to blunt Fresenius's showing on motivation. Among the hundreds of compounds synthesized by Dr. Stewart and affiliated researchers during the 1970s and 80s, Plaintiffs cherry-pick a single prior art example where an "Ac" (acetyl) group was added on top of an N-terminal D-Arg. JTX39.11. But Barabé does not suggest retaining the Fmoc on Fmoc-icatibant. First, Barabé does not address the use of Fmoc at all. Barabé discusses the use of acetyl, and as Dr. Walensky admitted, Fmoc is not an "acetyl" group; it is a urethane. Tr. 207:2-3, 504:10-15. In fact, the acetyl group described in Barabé is not listed among the Z or P groups of claim 1 of the '7,803 patent; it is a simpler chemical than the listed groups. *See* Tr. 588:23–589:12.

38. Second, the acetyl group in Barabé was added to reduce histamine release in a subset of bradykinin antagonists, not to reduce enzymatic breakdown of the peptides. Tr. 524:18–525:8. No evidence was presented suggesting histamine release was a concern with the icatibant peptide. Furthermore, the acetylation in Barabé produced mixed results—while it reduced histamine release, it created two other problems: agonistic activity and catecholamine release. Tr. 589:13–590:1, 525:4-12. Although the agonist activity could be reduced (though not eliminated) through further modification of the peptide sequence, there was no suggestion that the catecholamine release could be eliminated or even reduced. *Id.* Barabé's single outlier

compound would not have motivated a POSA to retain an Fmoc (or any of the other Z or P groups) as an N-terminal modification in addition to the N-terminal D-Arg. Tr. 133:19-22.

c. A POSA Would Have Had a Reasonable Expectation that the Icatibant Peptide Would Be a Bradykinin Antagonist

39. The POSA would have reasonably expected the icatibant peptide remaining after Fmoc removal would be a bradykinin antagonist based on its structure. A POSA would have first recognized the A through I portion of claim 1 of the '7,803 patent as a bradykinin antagonist peptide. *See supra* § II(A)(4). Once the Fmoc was removed, the icatibant peptide would be consistent with the prior art Stewart SAR data. In fact, the only difference from known potent prior art bradykinin antagonists, such as B-3824, would be at positions 7 and 8, where icatibant includes D-Tic at position 7 and Oic at position 8. Tr. 581:7-18. A POSA would have reasonably expected this structure to have bradykinin antagonist activity because these substitutions were consistent with the Stewart SAR data and the structure of prior art antagonists. Tr. 110:11-25; *supra* § II(A)(4). Indeed, Dr. Walensky admitted at trial that he selected prior art references to compare to the '7,803 claim because "they are patents that describe bradykinin antagonists." Tr. 598:22-25.

40. As discussed above, D-Tic is a conformationally constrained analog of D-Phe, which was an amino acid known to provide bradykinin antagonist activity when substituted at position 7, as in B-3824. *See supra* § II(A)(4). Oic is a conformationally constrained analog of proline, which was taught by Stewart as a substitution at position 8. *See supra* § II(A)(4). Based on to the prior art SAR, a POSA would have expected both of these amino acid substitutions to maintain bradykinin antagonist activity in the icatibant peptide.

d. Plaintiffs Fail to Undermine Reasonable Expectation of Success

41. Dr. Walensky expended considerable energy arguing that because D-Tic and Oic were

conformationally constrained, a POSA would not have a reasonable expectation of bradykinin antagonist activity in the resulting peptide. Here though, there is no question as to what particular amino acid a POSA would select; D-Tic and Oic are already included in claim 1 of the reference '7,803 patent. The icatibant peptide remaining after removal of the Fmoc is identical to the icatibant peptide of asserted Claim 14. Tr. 559:17-25. There is, in addition, no dispute that claim 2 of the '7,803 patent claims a method for treating inflammation using the claim 1 peptides as bradykinin antagonists. Tr. 594:1-21. Plaintiffs presented no evidence of a peptide being converted to a bradykinin antagonist by the addition of a Z or P group in addition to an N-terminal D-Arg.[6] Instead, the evidence showed that a POSA would have expected that the properties of the Fmoc-protected peptide arose from the peptide portion of the molecule, not the Z or P groups, and that a POSA would therefore have reasonably expected the bradykinin antagonist properties to be maintained without the Z or P groups. Tr. 127:23–128:11.

42. Even if claim 2 of the '7,803 patent is ignored, Dr. Walensky's position still fails. Dr. Walensky testified that conformational constraint could destroy peptide activity under certain circumstances and that a POSA would therefore have not have reasonably expected the D-Tic-and-Oic-substituted peptide to act as a bradykinin antagonist. But none of Dr. Walensky's testimony with respect to conformational constraint was tied to bradykinin antagonists. Further, on the basis of Dr. Stewart's SAR data, Dr. Walensky testified that proline—a naturally occurring conformationally constrained amino acid—was a viable substitution at both positions 7 and 8 of bradykinin antagonists. Tr. 598:10-21; JTX38.4 Table I (D-Pro at position

[6] Barabé, the single example that Plaintiffs identified of a protecting group on a D-Arg, discloses that the addition of the acyl group on the peptide had a negative effect on antagonist potency. Dr. Walensky testified that the antagonist activity was "essentially the same" between the analog with and without an acyl group on top of the D-Arg, and in fact the analog with the acyl group had a slightly lower measured potency. Tr. 526:19-24; *see also* Barabé, JTX39.11 Table V.

7); Tr. 547:21–548:3 ("cyclic amino acid[s] such as D- or L-Pro" at position 8); JTX38.3 at 4:44-48.

43. To the extent that a POSA were to, as Dr. Walensky suggests, focus on general teachings about constrained amino acid analogs in peptides other than bradykinin antagonists, the prior art suggested that researchers were substituting conformationally constrained analogs like Oic into various peptides without destroying activity. *See* Tr. 545:8-10 (Oic substitution was "around 2.3 times better"), 545:21–546:1 (Oic substitution had "the same" activity).

44. Dr. Walensky testified that the POSA would have been motivated to substitute D-Phe and Thi for D-Tic and Oic in the icatibant peptide, thus effectively going in reverse and re-creating the prior art bradykinin antagonist B-3824. Tr. 599:6–600:16. That is not what a POSA does. Given the previous use of conformationally constrained amino acids at positions 7 and 8 of bradykinin analogs, as well as the real-world activities of other researchers during the relevant time period, Dr. Walensky's hypothetical concerns over conformational constraints would not have plausibly blunted a POSA's expectation that icatibant would be a bradykinin antagonist.[7] The trial evidence showed that researchers at Nova working on bradykinin antagonists at approximately the same time considered constrained analogs to be viable substitutions in bradykinin antagonists—and in fact, a desirable strategy for *improved* antagonists. Tr. 635:15–

[7] At the end of his direct examination, Dr. Walensky quoted extensively from a chapter written by Dr. Stewart and his colleagues in 1979. The statements in that chapter and Dr. Walensky's related testimony are irrelevant to the issues in this case as the statements were made more than a decade before the priority date and years before Dr. Stewart and his group made the seminal discovery on how to create bradykinin antagonists and disclosed their extensive SAR data on the effects of changes in the bradykinin analogue sequence. *Compare* PTX250.1 (published in 1979) *with* JTX28.1 (application filed in 1985). Dr. Walensky's assertions regarding the uncertainty of making changes in a peptide are inapplicable as there are no changes to make; the amino acid sequences of the peptides in claim 14 of the '333 patent and claim 1 of the '7,803 patent are identical. Tr. 559:17-25.

636:21, 223:14-21. In its totality, the evidence at trial demonstrated that a POSA would have had a reasonable expectation that the icatibant peptide would have bradykinin antagonist activity.

6. Secondary Considerations Do Not Support a Finding of Nonobviousness

45. Plaintiffs' evidence of secondary considerations should not be given any weight because Plaintiffs have failed to demonstrate a nexus between the evidence proffered and the merits of the invention of claim 14 of the '333 patent. To the contrary, the trial evidence demonstrated that Plaintiffs' evidence of secondary considerations is irrelevant to the ODP question here. At the time of the invention of the '333 patent, a person in the real world would not have known of Fmoc-icatibant or any other peptides claimed in the '7,803 patent. The '7,803 patent was filed four years after the '333 patent and is not prior art. Tr. 785:3-14; DTX59.1; JTX1.2. Because Fmoc-icatibant was unknown, there is no basis to infer that others attempted to combine Fmoc-icatibant with the prior art and failed.

46. The trial evidence also showed that Hoechst, a worldwide pharmaceutical company, devoted approximately 12 years of time and significant financial resources to icatibant without developing a single commercial use. Hoechst began its bradykinin antagonist program between 1987 and 1988, and had synthesized icatibant by January 1989. Tr. 277:1-6, 450:3-14; PTX12.24. Hoechst's development of icatibant failed, however, and the peptide was eventually licensed out to Jerini, for essentially zero up-front investment. Tr. 303:25-305:22, 308:11-309:5; PTX36.9. By the time of Jerini's 2001 license, icatibant was "a dead compound sitting in the basement" at Hoechst, according to Dr. Knolle. Tr. 303:25-304:14. This twelve-year delay is objective, real-world evidence that factors other than the icatibant peptide itself—such as the method of treating HAE and/or the formulation for subcutaneous injection—were responsible for Firazyr becoming a viable drug product. Tr. 817:3-17. Plaintiffs' witnesses agreed that Hoechst was not focused on HAE as a potential indication at the time of the '333 invention, without

which there "would have been no sales or profits associated with Firazyr." Tr. 686:20-687:4, 432:21-433:21. Firazyr's subcutaneous formulation likewise required "a lot of work beyond just having icatibant." Tr. 433:7-17. Plaintiffs never addressed the degree to which these factors were responsible for any of Firazyr's success. *See* Tr. 687:5-17, 412:8-22, 415:4-16.

47. The trial evidence also demonstrated that the factors Shire uses to differentiate Firazyr are not novel to icatibant, but instead were also present in prior art bradykinin antagonists. Subcutaneous injection, stability, and tolerability are Firazyr's essential advantages over other treatments for acute HAE attacks. *See* Tr. 410:25-412:7, 413:3-414:3, 806:15-807:6; JTX43.32. Independent analysts identified "the ability to self-administer a room temperature stable, pre-filled syringe, upon initiation of an attack as the most significant differentiating factor for Firazyr versus its competition," and self-administration as the "holy grail" for acute HAE treatment. PTX155.5; JTX13.1.[8] However, these characteristics are not unique to icatibant. Prior art bradykinin antagonists could also be formulated for subcutaneous administration and were subcutaneously administered using the same formulation as icatibant with no differences in stability or tolerability. Tr. 137:6-139:9; DTX50.2-4; JTX28.7 at 12:33-35.

48. There was also no long-felt but unmet need fulfilled by the claimed icatibant peptide. Berinert, a drug used in Europe since the late 1970s, was also a safe, effective, and easily administered treatment for acute attacks of HAE. Tr. 425:6-16, 426:16-24 ("[W]hen Berinert came in, we were very excited about it. It was fast. It was safe. It was effective."). This treatment was available over a decade before icatibant was synthesized, and over two decades before development began on using icatibant to treat HAE. *Id.* Safe, effective, and easily administered treatments for acute attacks of HAE were also available in the US prior to Firazyr's approval.

[8] Shire presented no evidence that icatibant has safety or efficacy advantages. *Infra* ¶ 48.

Berinert and Kalbitor were both approved in the US in 2009, before Firazyr's 2011 approval. JTX21; JTX45; JTX47; Tr. 404:5-17, 406:15-20, 408:15-18. Dr. Kaplan's publication comparing acute HAE attack treatments rated Berinert and Kalbitor equal to Firazyr in safety and efficacy, DTX84.7; Tr. 435:15-436:19, 437:11-438:11, and Shire's 30(b)(6) witness testified that Firazyr had not been shown to be superior to other acute HAE attack treatments. Tr. 796:8-797:5, 799:17-25, 802:16-23; DTX120.8.[9]

49. There is also no evidence that the "commercial success" of Firazyr was driven by the characteristics of the icatibant peptide. With only a few thousand people undergoing treatment for HAE, third-party payers dedicate few resources to negotiating prices, allowing Shire to charge a high price. JTX12.25; Tr. 809:14-810:11, 810:20-811:2. As a result of these dynamics, Shire has achieved outsized profits on an extremely small number of patients. In 2016, the average Firazyr patient used over $200,000 of drug. Tr. 679:1-3. Fewer than a hundred patients are responsible for 40% of Firazyr sales, and approximately 16-20 patients each individually consume over $3,000,000 of Firazyr per year. Tr. 812:10-813:4; DTX298.56.

50. Rather than tout the advantages of the icatibant peptide, Shire drove sales by positioning itself as a leader in the market for HAE. Shire controls three of the five major drugs used to treat HAE, allowing Shire to control prevailing prices and manage the marketing attention within the HAE market. Tr. 679:3-25, 814:11-22. Accordingly, over 80% of Firazyr profits were realized after Shire gained control over the leading brands in both acute and prophylactic treatment of HAE. Tr. 680:4-23. Shire has also consistently priced Firazyr lower than the other acute HAE

[9] Berinert's effectiveness for laryngeal attacks was also known prior to Firazyr's US approval, because it was reported both on the Berinert label, JTX21.14; Tr. 427:12-428:13, and in publications, DTX76; 427:4-427:11, 428:14-429:17. Kalbitor was originally approved in 2009 for all acute attacks of HAE, including laryngeal attacks. JTX47.1, 8; Tr. 412:23-413:13.

treatments. For the entire time it has been on the market, Firazyr has been priced $1,000 to $3,000 less than competing treatments per attack. Tr. 675:16-676:16, 813:12-24; PTX92.

B. Conclusions of Law on Obviousness-Type Double Patenting

1. The Law of Obviousness-Type Double Patenting

51. Non-statutory obviousness-type double patenting prevents a later-expiring patent from covering an obvious variant of an earlier-expiring patent claim. *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1378 (Fed. Cir. 2014). It is a question of law. *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010).

52. The ODP analysis requires two steps. First, the court construes the claims and determines their similarities and differences. *AbbVie*, 764 F.3d at 1374; *Sun Pharm.*, 611 F.3d at 1384-85. Second, the court determines whether differences between the two claims are significant enough to render the later claim "patentably distinct" from the earlier claim. *AbbVie*, 764 F.3d at 1374. This analysis "entails determining, *inter alia,* whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1298 (Fed. Cir. 2012*)*.

53. This Court will be the first to analyze the ODP issue because it was never brought to the attention of the PTO. Hoechst never disclosed the copending '7,803 patent application to the '333 patent examiner during prosecution despite (i) the two applications containing nearly identical subject matter, and (ii) Hoechst's in-house patent attorney and outside patent counsel conducting in-person examiner interviews in both applications *on the very same day*. Tr. 781:1-22. Claim 14 of the '333 patent claims an obvious variant claim 1 of the '7,803 patent. Because the patents are co-owned and have inventors in common, the '7,803 patent is a proper ODP

reference. *See, e.g.*, *In re Hubbell*, 709 F.3d 1140, 1148 (Fed. Cir. 2013). Claim 14 of the '333 patent is therefore invalid for obviousness-type double patenting.

2. Claim Construction

54. Plaintiffs assert that claim 14 of the '333 patent should be construed in light of the patent's title, specification, and examples to include the phrase "having bradykinin antagonist activity." Tr. 554:23–555:15. But reading activity into claim 14 is wrong as a matter of law. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323-24 (Fed. Cir. 2005) (en banc). It is undisputed that the language of claim 14 describes the structure of a specific chemical compound, and that the claim language is clear and unambiguous. As stated by the *SmithKline* court, "[i]t would be difficult to imagine a more clear and definite claim." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339-40 (Fed. Cir. 2005) (rejecting attempt to read in limitations from specification where "this claim recites in clear terms a discernible chemical structure"). The clear, unambiguous language of claim 14 does not recite any type of activity for the claimed peptide, and the description of the peptide's activity in the specification does not give rise to any activity requirement: "[a] description of characteristics does not redefine a compound with an established and unambiguous structural definition." *Id.* at 1339.

55. Plaintiffs' arguments concerning the construction of claim 1 of the '7,803 patent are likewise flawed. Plaintiffs argue that claim 1 requires the Z group to be "permanent," "integral," or part of a "final" peptide. Tr. 500:18-24. But reading in these limitations from the patent specification is wrong as a matter of law for the same reasons it is wrong to read activity into claim 14 of the '333 patent. The language of claim 1 of the '7,803 patent describes a genus of chemical compounds, and that language is unambiguous. Plaintiffs' argument is another attempt to have the Court rely on and read in limitations from the '7,803 patent specification.

56. Plaintiffs' positions on claim construction are also inconsistent. To the extent any

components of the peptides of Claim 1 of the '7,803 patent are "permanent," "integral," or part of a "final" product, they would surely be the D-Tic at position 7 and the Oic at position 8. Yet Dr. Walensky suggested repeatedly that a POSA would have been motivated to substitute different amino acids at those positions. *See, e.g.*, Tr. 530:25–531:5, 538:25–539:4. And while Plaintiffs suggest reading an activity requirement into the clear and unambiguous language of claim 14 of the '333 patent, they do not make that argument regarding the equally clear and unambiguous language of claim 1 of the '7,803 patent. The reason is clear: if claim 1 of the '7,803 patent—which undisputedly covers Fmoc-icatibant—were construed to have bradykinin antagonist activity, then Plaintiffs could not argue that the POSA would not expect icatibant to have that same activity. In fact, if the '7,803 patent specification could be considered, then it discloses that Fmoc-icatibant has bradykinin antagonist activity and that icatibant itself has bradykinin antagonist activity (by citing the European priority application of the '333 patent). Tr. 746:1-7 (listing European patent equivalents to the '333 patent); DTX59.1 at 1:9-11 (listing same); DTX59.8.

3. Claim 1 of the '7,803 Patent Claims Fmoc-Icatibant

57. A lead compound analysis is not required to prove ODP for claims directed to a chemical compound because the analysis simply begins with any compound claimed in the earlier-expiring patent. *Otsuka*, 678 F.3d at 1297. Here, there is no dispute that claim 1 of the '7,803 patent claims Fmoc-icatibant. Hence, the proper legal analysis begins with Fmoc-icatibant.

58. But even if a lead compound analysis was required, Dr. Bachovchin explained that a POSA would have focused first on Fmoc-icatibant. Not only is Fmoc-icatibant the first species in the '7,803 patent genus, but as discussed above, based on the prior art, a POSA would have focused first on Fmoc at Z, nothing in the P position, D-Arg at position 0, and Oic at position 8, which would yield Fmoc-icatibant. *Supra* § II(A)(4). Plaintiffs offered no evidence that Fmoc-icatibant

would not be a reasonable compound for a POSA to select from claim 1 of the '7,803 patent.

4. Fresenius Presented Clear and Convincing Evidence that the Differences Between the Claims Are Insubstantial

59. As discussed above, the only difference between claim 1 of the '7,803 patent and claim 14 of the '333 patent is the presence or absence of the extra N-protecting groups—the Z and P groups. *Supra* § II(A)(5). The only difference between Fmoc-icatibant and icatibant is the presence of the Fmoc. Fresenius presented clear and convincing evidence demonstrating that a POSA would have been motivated to remove the Fmoc, and that they would have had a reasonable expectation that the resulting peptide would be a bradykinin antagonist.[10] *Id*.

a. Fresenius Demonstrated a Motivation to Remove Fmoc by Clear and Convincing Evidence

60. "To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). Here, the clear and convincing evidence showed that Fmoc was a group that was made to be removed. Tr. 107:24–108:8. Fmoc was the most common protecting group used in solid-phase synthesis, where it would be removed from the peptide dozens of times. Tr. 75:7-13, 105:1-4, 154:17–155:2; DTX60.4.

61. The prior art taught that no additional N-terminal group beyond a D-Arg was required for bradykinin antagonist activity, making the Fmoc superfluous. *See supra* § II(A)(5)(b); *see also* Tr. 126:22–127:5. One of the most potent prior art bradykinin antagonists, B-3824, had no such

[10] If the Court rejects the Plaintiffs' proposed construction of claim 14 of the '333 patent to require "bradykinin antagonist activity," then the test for reasonable expectation of success would not require an expectation that the peptide remaining after removal of the Fmoc (or any other Z or P group) would have that activity. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Nevertheless, the POSA would have had that expectation based on the extensive bradykinin antagonist prior art presented at trial.

N-terminal groups beyond the D-Arg. *See id.*; *see also* Tr. 127:1-9, 581:7-24. And Dr. Stewart's publications, SAR data, and hundreds of published examples of antagonists all suggested that a D-Arg at the N-terminus was sufficient to provide resistance to aminopeptidase enzymes. *Supra* § II(A)(5)(b). Shire's reliance on a single reference disclosing a single Acetyl-D-Arg compound does not undermine that conclusion in any way, as the reference did not disclose Fmoc (or any other Z or P group) and detailed problems caused by the N-terminal addition. *Id.*

62. On the basis of the '7,803 patent specification and the prior art, Plaintiffs tried to show that a POSA would think an N-terminal Fmoc might, under some circumstances, have some beneficial effects on some peptides. But the specification of the '7,803 patent is irrelevant as a matter of law to the analysis of ODP. Obviousness-type double patenting determinations generally turn on a comparison between the claims of the earlier-expiring and later-expiring patents, and the specification of the earlier-expiring patent is generally not considered. *See Sun Pharm*, 611 F.3d at 1387; *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1380 (Fed. Cir. 2012) (ODP analysis "turns on an evaluation of what [patentee] has claimed, not what it has disclosed").[11] Dr. Walensky's opinions based on the specification of the '7,803 patent are legally irrelevant.

63. Dr. Walensky's argument that claim 1 should be construed to require the Z group to be "permanent," or "integral," or part of a "final compound" is likewise legally flawed. The possibility that a Z or P group could potentially provide some benefit in some situations does not undermine the overwhelming evidence of motivation to remove the group in this case. Because

[11] Limited exceptions to this rule exist for compound patents, designed to avoid the situation where a patent holder can unfairly extend the life of an earlier-expiring compound patent through new patent claims covering the methods of use already disclosed in the earlier-expiring patent's specification. *See id.* at 1378-80. Those exceptions are not applicable in this case.

of Fmoc's common use in peptide synthesis and ease of removal, a POSA looking at the structure of Fmoc-icatibant would have seen the difference between Fmoc-icatibant and icatibant as "trivial" and "of no real significance," and would have been interested in the properties of the key structure—the ten-amino-acid icatibant peptide. Tr. 109:23–110:2, 127:23–128:11.

b. Fresenius Demonstrated by Clear and Convincing Evidence A Reasonable Expectation That Icatibant Would Be A Bradykinin Antagonist

64. Fresenius also demonstrated that a POSA looking at the structure of icatibant would have had a reasonable expectation that it would be a bradykinin antagonist, based on the structure of the molecule and the prior art SAR data, and alternatively on Claim 2 of the '7,803 patent. D-Tic at position 7 and Oic at position 8 are consistent with Dr. Stewart's SAR data and the sequence of prior art bradykinin antagonists. *Supra* § II(A)(5)(c).

65. Plaintiffs' argument—that a POSA would return to substitutions already tested by Dr. Stewart rather than test icatibant—makes no sense in the real world. Essentially, Plaintiffs are arguing that a POSA would have no *guarantee* that conformationally constrained substitutions would work, and therefore would be so afraid to try them that they would revert to the prior art before trying icatibant. *Supra* § II(A)(5)(d). But "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). The law does not require "[c]onclusive proof of efficacy." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Fresenius showed that a reasonable expectation existed that icatibant would be a bradykinin antagonist. *Supra* § II(A)(5)(c).

5. Secondary Considerations Cannot Save the Validity of Claim 14

66. Long-felt need and commercial success both seek to show that others were motivated to solve the problem of the invention but were not successful. *Subtests of "Nonobviousness": A*

Nontechnical Approach to Patent Validity, 112 U. Pa. L. Rev. 1169, 1172-77 (1964), *cited by Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). Long-felt need relates to obviousness because a fact-finder can infer the failure of others to achieve the invention. "Existence of the defect creates a demand for its correction, and it is reasonable to infer that the defect would not persist were the solution 'obvious.' This is the rationale of long-felt demand and its justification as a test of nonobviousness." *Id.* at 1172-73; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). The same rationale also underlies commercial success. *Subtests*, 112 U. Pa. L. Rev. at 1175; *see also Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

67. Although there is no *per se* rule prohibiting the assertion of long-felt need or commercial success in the context of ODP, *see Eli Lilly v. Teva*, 689 F.3d at 1381, evidence of secondary considerations is not probative to an obviousness inquiry if the facts presented provide no logical basis to connect the consideration to whether the invention was obvious. *Merck*, 395 F.3d at 1376-77 ("chain of inferences" connecting commercial success to obviousness "fails" when others would not have been induced to attempt to solve the problem of the invention).

68. Here, evidence of commercial success or long-felt need is irrelevant to the ODP issue. Because a POSA at the time of the invention never had an opportunity to combine the prior art with Fmoc-icatibant (then unknown in the field), there is no basis to use evidence of long-felt need or commercial success to infer that a POSA attempted to combine Fmoc-icatibant with the prior art and failed. The "chain of inferences fails on these facts." *Id.*; *see also Subtests*, 112 U. Pa. L. Rev. at 1173. Without an alternative rationale to infer that evidence of long-felt need or commercial success is relevant to the ODP inquiry, there can be no nexus. But Plaintiffs neither proved nor presented any such alternative rationale. Instead, Plaintiffs simply asserted that the

application of secondary indicia is "exactly the same" in the context of obviousness and obviousness-type double patenting. D.I. 103 (Tr. of Jan. 23, 2018 Pretrial Conference) at 11:1-8. Under these circumstances, the evidence at trial does not establish a nexus.

69. The critical importance of the HAE treatment method and subcutaneous formulation to Firazyr's performance also obstructs any nexus to claim 14 of the '333 patent. Hoechst was unable to develop a commercially viable icatibant product despite working with the compound for over a decade. Hoechst's abandonment of icatibant is objective evidence that factors such as the development of the method of treating HAE and/or the formulation for subcutaneous injection were critical to Firazyr's ultimate performance, not characteristics of the claimed icatibant peptide. *See In re Cree, Inc.,* 818 F.3d 694, 703-04 (Fed. Cir. 2016) (finding no nexus when a subsequent technological development was critical to the product's performance). Hoechst's inability to commercialize icatibant after 12 years demonstrates that the success of Firazyr cannot be attributed solely to icatibant itself.

70. Additionally, none of the secondary indicia are attributable to a novel aspect of the '333 patent. "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *Novartis AG v. Torrent Pharm. Ltd*., 853 F.3d 1316, 1330 (Fed. Cir. 2017). The evidence showed that the advantages of Firazyr (subcutaneous injection, stability and tolerability) were also properties of prior art bradykinin antagonists. There can be no nexus because any secondary considerations do not result from novel aspects of claim 14.

71. Plaintiffs also failed to establish a long-felt need satisfied by the '333 patent. Even if there is evidence that the "claimed [invention] may have been beneficial," that evidence is not probative if "others had previously solved the long-felt need." *In re PepperBall Techs., Inc*., 469

F. App'x 878, 882-83 (Fed. Cir. 2012). Because Firazyr was not the first safe, effective, and easily administered treatment for acute attacks of HAE, it did not satisfy a long-felt need for such a treatment. Moreover, if a long-felt need or commercial opportunity for HAE treatments had been felt in 1989, it would have been directed towards bringing Berinert—a known treatment for HAE—to the US. There is no basis to conclude that such motivations would have driven the development of icatibant, a compound associated with other conditions for over a decade.

72. In addition to defects in Plaintiffs' nexus arguments that apply to both secondary considerations, the evidence further showed that there is no nexus to Firazyr's commercial performance because of the nature of the HAE market. Shire's leadership in that market and Shire's pricing strategy each played essential roles in Firazyr's commercial performance. *Supra* § II(A)(6). A patentee cannot satisfy its burden of establishing a nexus between any alleged commercial success and the claimed invention where significant sales are due to factors other than the merits of the patented invention. *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

III. PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW ON PROSECUTION LACHES

A. Findings of Fact on Prosecution Laches

73. The first U.S. application leading to the '333 patent was filed on June 30, 1989. Tr. 326:19-24; JTX6A.4. The '333 patent issued on July 15, 1997 and it expires on July 15, 2019, more than 30 years after the first application was filed. JTX2.391. The undisputed trial evidence showed that during the prosecution of the '333 patent, without any plausible explanation or reasoning, applicants spent more than four years—half of the total prosecution of the patent—failing to provide a single substantive response to the PTO, thereby delaying the issuance and extending the term of the patent, which expires seventeen years from issuance.

1. The Trial Evidence Showed A Four-Year Delay In Prosecution

74. The applications leading to the '333 patent were divided into three different groups based on the sequence of the disclosed peptides. Tr. 326:25-328:9, 328:14-329:5. Each group was directed to bradykinin antagonist peptides, but there were minor differences in the peptide sequences. *Id*. The applications in each group were initially prosecuted in parallel, but even though the applications were not prior art to each other, there were repeated ODP rejections by the PTO between the groups. *See, e.g.*, JTX6A.474. Hoechst eventually combined all three groups rather than try to overcome the ODP rejections based on distinctions between the amino acid sequences. Tr. 335:7-22, 716:22-717:11, 783:2-784:8. The '333 patent issued from an application resulting from the combination of all three groups. Tr. 716:24-717:25; *see* JTX7A.

75. The specification of the first application, the '162 application, included *in vitro* data for some peptides, but it did not include *in vivo* data. Tr. 317:23-319:17. The PTO issued the first Office Action on August 17, 1990; it contained multiple rejections, including a §101 "utility" rejection. JTX6A.152-159; Tr. 319:18-320:8, 320:16-22, 323:20-23. The Examiner rejected the application under §101 on the basis that the *in vitro* data included in the application was insufficient to show utility, and specifically requested *in vivo* data related to the claimed peptides. JTX6A.154-155; Tr. 319:18-320:8, 320:16-22.

76. On February 17, 1991, Hoechst responded to each of the rejections. Tr. 323:24-324:23; JTX6A.221-240. Although Hoechst had *in vivo* data before it filed the first U.S. application, it did not provide any such data in response to the §101 rejection. Tr. 320:23-323:19, 323:24-324:18, 472:9-474:6, 474:12-476:9; DTX50. Instead, Hoechst argued the *in vitro* data provided in the specification was sufficient to demonstrate utility. JTX6A.231-234; Tr. 323:24-324:18.

77. The Examiner disagreed, and Hoechst received a Final Office Action on May 31, 1991. JTX6A.247-255; Tr. 324:24-325:7. The Final Office Action contained multiple rejections,

including the same §101 rejection and request for *in vivo* data. JTX6A.247-255; Tr. 323:24-326:9. Hoechst did not respond to the Final Office Action in the '162 Application, but instead filed a continuation-in-part application. Tr. 330:10-12, 323:24-326:9; JTX6A.330.

78. Following the May 31, 1991 Office Action in the '162 Application, Hoechst did not substantively respond to any office actions until June 6, 1995—a period of over four years. *See generally* JTX3; JTX4; JTX5A; JTX6A; JTX7A. Though the trial evidence focused on Hoechst's failure to provide *in vivo* data responsive to the repeated §101 rejections, Hoechst did not address any of the rejections advanced in the nine office actions issued during this four year period. *Id.*

79. Instead of responding to the pending office actions, Hoechst filed eight continuation or continuation-in-part applications. These continuation and continuation-in-part applications did not scientifically address the rejections in the office actions. Tr. 359:18-360:2. And while it filed continuation-in-part applications adding *in vitro* data to the specification during the four-year period of delay, Hoechst never added the *in vivo* data its possessed. *See, e.g.*, Tr. 330:10-331:18. In total, Hoechst failed to respond to any office actions in eight of the eleven applications in the '333 patent prosecution history—the '270, '297, '149, '090, '766, '523, '052, and '849 Applications. Tr. 328:14-329:12, 331:22-333:7, 333:11-337:20.

2. Applicants' Four-Year Delay Was Unreasonable and Unexplained

80. Hoechst was in possession of the *in vivo* data requested by the Examiner at least as early as March 1989, *i.e.*, prior to the original '162 application filing date. *See* PTX12.140-142; PTX12.160; Tr. 472:9-474:6, 474.12-476:9, 763:18-764:2. Hoechst submitted this data for publication as early as July 25, 1990, and it was published in 1991, as part of Wirth 1991. *See* DTX50; PTX12.140-142; PTX12.160; Tr. 472:9-474:6, 474.12-476:9, 763:18-764:2.

81. Hoechst finally responded to an office action on June 6, 1995. JTX7A.263; Tr. 339:17-

340:6. While Hoechst continued to argue that the *in vitro* data in the specification should be sufficient, for the first time, Hoechst also submitted a declaration from Dr. Schölkens, an inventor on the '333 patent, "to address the Examiner's specific concerns" about the predictive value of the bradykinin antagonists *in vivo*. Tr. 340:23-341:18, 764:3-765:17; JTX7A.298-302; JTX7A.327-331. The Schölkens declaration cited only two papers to support the conclusion that "a compound that counteracts [the] effect of bradykinin *in vivo* in an animal model can be reasonably predicted to be effective *in vivo* in treating asthma." JTX7A.329-330.

82. The Schölkens declaration cited Wirth 1991, which contained *in vivo* results for icatibant. Tr. 320:23-323:19, 341:7-342:11; JTX7A.327-331; DTX50. Dr. Wirth admitted that some of the *in vivo* data in Wirth 1991 had been in Hoechst's possession since March 1989. *See* PTX12.140-142; PTX12.160; Tr. 472:9-474:6, 474.12-476:9; *see also* Tr. 760:2-16.

83. As explained by Dr. Raines, there is no scientific reason or explanation why Hoechst could not have provided this *in vivo* data to the PTO in response to the original August 17, 1990 Office Action. Tr. 342:12-15. And Plaintiffs provided no explanation at trial. *See* Tr. 760:2-16, 766:2-5.

84. The Dr. Schölkens declaration also cited a confirmatory 1993 Wirth paper. Tr. 342:16-343:15; JTX7A.342-346. The *in vivo* data in Wirth 1993 was available to Hoechst at least as early as December 16, 1991. Tr. 343:16-344:10, 762:25-763:6; JTX7A.342. There is no scientific reason or explanation why Hoechst could not have provided this *in vivo* data to the PTO as early as December 16, 1991. Tr. 343:16-344:10, 763:18-764:2. Plaintiffs similarly failed to provide any such explanation at trial. Tr. 763:18-764:6, 766:2-5.

85. Once Hoechst provided the requested *in vivo* data, the PTO immediately withdrew the §101 rejection. Tr. 345:8-346:1; JTX7A.429. Dr. Raines testified that there was no reason why the arguments and responses to the non-§101 rejections could not have been made earlier. Tr. 348:1-

5, 348:16-20. After Hoechst began to substantively respond to office actions, the '333 patent was allowed in approximately 18 months. Tr. 347:11-14; JTX2.224.

86. At trial, Plaintiffs offered no explicit explanation for this delay. To the extent Plaintiffs now proffer an explanation in their briefing, any such post-hoc explanation should be rejected.

87. Plaintiffs suggested that Hoechst's delay was caused by internal strategies that the company had regarding patent prosecution. Tr. 704:24-705:13, 724:19-725:1, 726:10-19, 735:21-24. But Dr. Wingefeld, the individual responsible for prosecution of the '333 patent applications, confirmed that she could not recall whether Hoechst's general prosecution strategies applied to the prosecution of the '333 patent. Tr. 766:2-13. Also, when asked why Hoechst did not present arguments in response to office actions sooner, Dr. Wingefeld stated "I don't recall why specifically we didn't do this." Tr. 766:5. Moreover, there was no explanation for why these strategies would provide a legitimate explanation for failing to provide any substantive response for more than four years.

88. Dr. Wingefeld also suggested that the delay arose because Hoechst had limited *in vivo* data. Tr. 726:10-19. But there is no question that Hoechst had the icatibant *in vivo* data in 1989. *See* PTX12.140-142; PTX12.160; Tr. 472:9-474:6, 474.12-476:9. And Dr. Wirth, the scientist responsible for *in vivo* testing of bradykinin antagonist peptides at Hoechst, confirmed that *in vivo* testing on compounds was generally conducted for compounds that show activity in *in vitro* assays. Tr. 470:17-471:7. The application leading to the '7,803 patent, for example, included *in vivo* data for six compounds. Tr. 757:8-758:10. Moreover, Hoechst eventually submitted the *in vivo* data for icatibant only and overcame the §101 rejection.

89. Plaintiffs may also argue a change to the PTO's utility guidelines as a reason for the delay. But these guidelines *lowered* the standard for utility; in light of that, there would be no reason to

suddenly submit *additional* data to meet this new lower standard. *Compare* PTX72 *with* PTX74. Yet that is what the applicants did. JTX7A.298-300; Tr. 764:3-765:17. The change in the guidelines offers no explanation for why applicants did not submit the *in vivo* data earlier.

90. Plaintiffs also pointed to the Examiner's citation of Wirth 1991 as evidence that the Examiner knew about the earlier *in vivo* data on icatibant. Tr. 759:24-760:16. The evidence at trial established, however, that despite receiving rejections under § 102(f) in light of Wirth 1991, Hoechst did not explain to the PTO that the paper contained *in vivo* data relevant to the §101 rejection until June 6, 1995. *Id*. When Hoechst did finally point out the data in response to the §101 rejection, the rejection was immediately withdrawn. Tr. 345:8-20; JTX7A.429.

91. The more reasonable inference is that Hoechst finally provided a substantive response on June 6, 1995 because the adoption of GATT eliminated any advantage from a further delay in prosecution. On December 8, 1994, GATT was signed into law in the U.S. GATT changed the term of patents filed on or after June 8, 1995, to 20 years from the filing date of the original application. *Id.* For earlier filed applications, patents received a 17-year term from the date of issuance or 20 years from the filing date, whichever was longer. *Id.*

92. After four years of filing serial continuation applications in lieu of responding to office actions, Hoechst finally responded to an office action in the '018 Application on June 6, 1995—the first response after GATT was signed into law. JTX7A.263-314; Tr. 357:14-25. The next day, on June 7, 1995, Hoechst also filed the '442 continuation application. JTX2.2-5. Both of these applications had the same specification and claims, and if granted, either would take advantage of the longer patent term of 17-years from issuance. JTX2.6-105; JTX7A.8-110.

3. Nova Was Working on Bradykinin Antagonists Within the Scope of the '333 Patent During Hoechst's Period of Delay

93. The evidence at trial clearly showed that scientists at Nova were synthesizing bradykinin

antagonist peptides before and during Hoechst's period of delay. Nova had in-licensed bradykinin antagonist peptides from Dr. Stewart in the 1980s. Tr. 219:2-12. Nova altered the amino acid sequence of earlier peptides in an effort to develop bradykinin peptides that were more resistant to enzymatic degradation. *See, e.g.*, Tr. 220:3-20, 228:17-229:14, 621:9-624:6. The goal of this synthesis was to develop new peptides for therapeutic use. Tr. 228:11-21.

94. As part this program, scientists at Nova independently developed NPC 16731 before Nova was aware of Hoechst's work on the same peptide. JTX9; Tr. 232:10-235:16, 618:6-619:23, 629:11-632:4, 634:23-635:14. NPC 16731 is the same peptide as Example 48 in the '162 Application, was covered by Group I (and the combined Group) patent claims throughout the prosecution of the '333 patent applications, and is covered explicitly by at least claim 12 of the '333 patent. JTX1.24; JTX6A.38; *see generally* JTX2; JTX6A; JTX7A; Tr. 350:25-351:25. NPC 16731 became Nova's "standard peptide," and despite budgetary constraints and interest in other projects, Nova continued to work on this and other bradykinin antagonist peptides until at least 1993, which is during the period of Hoechst's prosecution delay. Tr. 216:7-22, 238:16-239:5, 616:10-20; JTX41; JTX9.

95. Plaintiffs may suggest that Nova abandoned its bradykinin antagonist project prior to the period of delay, but Hoechst's own internal documents continue to reference Nova as its main competitor into the period of delay. PTX61; PTX61T.7; Tr. 480:1-481:9. Hoechst was aware of Nova's work on bradykinin antagonists and communicated with Nova about it. *See, e.g.*, Tr. 750:6-9; PTX58. In fact, Hoechst followed Nova's presentations closely and added *in vitro* data for NPC 16731 to the Hoechst patent applications only *after* scientists at Nova had published on it. JTX41; Tr. 769:24-772:3, 772:5-774:3, 774:4-22; JTX6A-221-240; PTX58. To the extent Plaintiffs suggest that Nova copied this compound from Hoechst (*see* Tr. 245:1-

249:4), the trial evidence established that scientists at Nova scientists independently synthesized NPC 16731. Tr. 232:10-235:16, 618:6-619:23, 629:11-632:4, 634:23-635:14; JTX9. Dr. Burch and Dr. Kyle co-authored a paper in the Journal of Medicinal Chemistry that explained "[NPC 16731] was discovered coincidentally and independently in our laboratories." JTX9.3-4.

4. The Extension of the '333 Patent Term Caused by Hoechst's Delay Prevents Earlier Regulatory Approval of Fresenius's ANDA

96. The NDA for Firazyr was approved on August 25, 2011. The FDA determined that Firazyr was entitled to NCE until August 25, 2016. Fresenius filed its ANDA for a generic version of Firazyr on the earliest possible date an ANDA could be filed, the so-called "NCE-1" date, which was August 25, 2015. Uncontested Facts ¶ 23. Shire obtained the maximum patent term extension of five years for the '333 patent. JTX2.390-391. Firazyr was also granted a 7-year period of ODE by the FDA, which expires August 25, 2018. The ODE expiration is the earliest possible date that Fresenius's product can be approved. 21 C.F.R. § 316.31. But for applicants' four year delay in prosecution of the '333 patent, which extended the term of the patent until July 15, 2019 (including the patent term extension), the FDA could approve Fresenius's ANDA on August 25, 2018, and Fresenius could launch its product immediately thereafter.

B. Conclusions of Law on Prosecution Laches

97. Prosecution laches has two elements: (a) unreasonable and unexplained delay by an applicant during prosecution, and (b) prejudice. *Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724 (Fed. Cir. 2010); *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 422 F.3d 1378 (Fed. Cir. 2005). Both elements are satisfied here.

98. There is no dispute that after May 31, 1991, Hoechst initiated a pattern of filing continuation applications in lieu of responding to office actions that lasted more than four years. *See generally* JTX3; JTX4; JTX5A; JTX6A; JTX7A. The applicants' reasoning for this delay

was not explained at trial. At most, Plaintiffs offered unsupported theories in lieu of reasons, but at the end of the day, Dr. Wingefeld, Hoechst's in-house patent attorney overseeing the prosecution of the '333 patent, could only say: "I don't recall why specifically we didn't do this." Tr. 766:5. In *Symbol Technologies*, the Federal Circuit addressed the difference between legitimate refiling of patent applications and filings made for the business purpose of delay. 422 F.3d at 1385; *see also Cancer Research Tech. v. Barr Labs., Inc.*, 679 F.Supp. 2d 560, 575 (D. Del. 2010) (finding delay could not be "'explained by reference to [] legitimate considerations and/or expectations'") (citation omitted), *rev'd on other grounds*, 625 F.3d 724, 729 (Fed. Cir. 2010). Plaintiffs offered no evidence of a legitimate reason for their pattern of delay.

99. Hoechst's delay was unreasonable. The trial evidence showed that Hoechst had the data and information requested by the Examiner in the first office action and simply did not provide it, despite providing the very same kind of evidence in the copending '7,803 patent application. *See, e.g.*, DTX55.169-173. Furthermore, it is undisputed that Hoechst only began substantively responding to office actions after the U.S. signed onto GATT. In the two days before the GATT legislation effective date, applicants (i) responded to a pending office action for the first time in over four years, and (ii) filed another continuation application to increase chances of receiving a longer patent term based on a pre-GATT filing date. The timing of the responses makes clear Hoechst's motive: extending the patent term.

100. "[T]o establish prejudice an accused infringer must [also] show evidence of intervening rights, *i.e.*, that either the accused infringer or others invested in, worked on, or used the claimed technology during the period of delay." *Cancer Research*, 625 F.3d at 729. Fresenius offered clear and convincing evidence of prejudice to Nova under *Cancer Research*. Prior to and during applicants' period of delay, Nova was synthesizing bradykinin antagonists for pharmaceutical

development. At least one of Nova's potent bradykinin antagonists, NPC 16731, is exemplified in and claimed by the '333 patent. JTX1.14, 24. The testimony of Drs. Burch and Kyle, along with Nova publications, detail the work performed by Nova scientists on bradykinin antagonists, including NPC 16731, until at least 1993. *See, e.g.*, Tr. 216:7-22, 616:10-20. Plaintiffs suggested at trial that Nova was not causally harmed by Hoechst's prosecution delay. But no causal link is required to show prejudice under *Cancer Research*. 625 F.3d at 729. The unrebutted evidence clearly establishes prejudice as Nova was working NPC 17631 during the period of delay.

101. Fresenius is also prejudiced by Hoechst's prosecution delay. In *Cancer Research*, the Federal Circuit found that the generic defendant was not prejudiced because while it legally could have filed its ANDA four years after the NDA approval, it did not do so until many years later, and the patent at issue did not receive the full five years of patent term extension. *Id.* at 731-732. It is undisputed that Fresenius filed its ANDA on the NCE-1 date, the first date it legally could have filed its ANDA, and the '333 patent received a full five years of patent term extension. Thus, the bases on which the Federal Circuit previously rejected the generic defendant's showing of prejudice do not exist here. *Id*. If applicants had not delayed prosecution for four years, the '333 patent would be expired and would not block FDA approval of Fresenius's ANDA product beyond the Orphan Drug Exclusivity date.

IV. RELIEF REQUESTED

Fresenius respectfully requests that judgment be entered in its favor on its affirmative defenses and counterclaims that claim 14 of the '333 patent is invalid under the doctrine of obviousness-type double patenting and unenforceable under the doctrine of prosecution laches, that Plaintiffs' claim of infringement of the '333 patent be dismissed with prejudice, and that all relief requested by Plaintiffs concerning the '333 patent be denied. Fresenius also respectfully requests that it be awarded its costs.

Respectfully submitted,

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